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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 25

Application Number	**10/762,588**
Filing Date	**January 21, 2004**
First Named Inventor	**TCHAGA, GRIGORIY S.**
Group Art Unit	**1656**
Examiner Name	**ROOKE, AGNES BEATA**
Attorney Docket Number	**CLON-056US2**

ENCLOSURES (check all that apply)

- [☒] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment / Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Documents
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [☒] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [☒] Other Enclosure(s) *(please identify below):*
  USPTO Credit Card Payment Form; Postcard25

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Signing Attorney/Agent (Reg. No.)	**BRET E. FIELD, 37,620** **BOZICEVIC, FIELD & FRANCIS, LLP**
Signature	
Date	**February 6, 2007**

EXPRESS MAIL LABEL NO. EV687639175US

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/17 (07-06)
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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2006

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

Complete if Known	
Application Number	10/762,588
Filing Date	January 21, 2004
First Named Inventor	TCHAGA, GRIGORIY S.
Examiner Name	ROOKE, AGNES BEATA
Art Unit	1656
Attorney Docket No.	CLON-056US2

METHOD OF PAYMENT (check all that apply)

☐ Check ☒ **Credit Card** ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: **50-0815** Deposit Account Name: **Bozicevic, Field and Francis LLP**

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims _____ - 20 or HP = _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20

Indep. Claims _____ - 3 or HP = _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3

Multiple Dependent Claims: Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = Extra Sheets _____ / 50 = Number of each additional 50 or fraction thereof _____ (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S)

	Fee Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other: **Appeal Brief**	500.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 37,620	Telephone 650-327-3400
Name (Print/Type)	Bret E. Field		Date 02/06/2007

VIA EXPRESS MAIL

EV687639175US

APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/762,588
	Confirmation Number	3721
	Attorney Docket No.	CLON-056US2
	Filing Date	January 21, 2004
	First Named Inventor	Tchaga, Grigoriy S.
	Examiner	Rooke, Agnes Beata
	Group Art	1656
	Title: *Methods and Compositions for Protein Purification*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated August 10, 2006. No claims have been allowed. Claims 11-13; 16; 18-21; 23 and 24 are pending and appealed herein. A Notice of Appeal was filed on December 11, 2006, making an Appeal Brief due on February 11, 2007. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. CLON-056US2.

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TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Clontech Laboratories, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on January 21, 2004 with Claims 1-17. During the course of prosecution, Claims 18-24 were added and Claims 1-10, 14-15, 17, and 22 were canceled. Accordingly, Claims 11-13, 16, 18-21, 23 and 24 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to kits for purifying proteins that include a metal ion affinity peptide.

Below is a description of each appealed claim and the location in the specification where support for each claim can be found (in parentheses). The provided location for support is given as exemplary and is not intended to be exhaustive.

Claim 11 claims a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for

inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide (see specification at page 12, paragraph [0051], page 29, paragraph [00111] and page 36, paragraphs [00137] and [00139]).

Claim 12 claims the kit in Claim 11, in which the first metal ion is a hard metal ion, and the second metal ion is an intermediate metal ion (see specification at page 14, paragraph [0059]).

Claim 13 claims the kit in Claim 12, in which the hard metal ion is chosen from Fe^{3+}, Ca^{2+} and Al^{3+}; and the intermediate metal ion is chosen from Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+} (see specification at page 14, paragraph [0059]).

Claim 16 claims the kit in Claim 11 where the kit further includes: an extraction buffer, a wash buffer and an elution buffer (see specification at page 36, paragraph [00137]).

Claim 18 claims a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion, a second composition including a second metal ion chelate resin including a second immobilized metal ion, and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide (see specification at page 12, paragraph [0051], page 14, paragraph [0060], page 29, paragraph [00111] and page 36, paragraphs [00137] and [00139]).

Claim 19 claims the kit in Claim 18, in which the second metal ion is a hard metal ion (see specification at page 14, paragraph [0059]).

Claim 20 claims the kit in Claim 19, in which the hard metal ion is chosen from Fe^{3+}, Ca^{2+} and Al^{3+} (see specification at page 14, paragraph [0059]).

Claim 21 claims the kit in Claim 18 where the kit further includes an extraction buffer, a wash buffer and an elution buffer (see specification at page 36, paragraph [00137]).

Claim 23 claims the kit in Claim 11, in which the metal ion affinity peptide comprises SEQ ID NO:1 (see specification at pages 24 and 25, paragraph [0092]).

Claim 24 claims the kit in Claim 18, in which the metal ion affinity peptide comprises SEQ ID NO:1 (see specification at pages 24 and 25, paragraph [0092]).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 11-13, 16, 18-21 and 23-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630).

ARGUMENT

Claims 11-13, 16, 18-21 and 23-24 are not obvious under 35 U.S.C. § 103(a) over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630).

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 11, 16 and 23, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide;

Group II: Claim 12, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; in which the first metal ion is a hard metal

ion, and the second metal ion is an intermediate metal ion; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide;

Group III: Claim 13, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; in which the first metal ion is a hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}, and the second metal ion is an intermediate metal ion chosen from Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide;

Group IV: Claims 18, 21 and 24, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion, a second composition including a second metal ion chelate resin including a second immobilized metal ion, and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a

fusion partner protein for the metal ion affinity peptide;

Group V: Claim 19, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion, a second composition including a second metal ion chelate resin including a second immobilized hard metal ion, and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide;

Group VI: Claim 20, drawn to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion, a second composition including a second metal ion chelate resin including a second immobilized hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}, and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide; and

Group I: Claims 11, 16 and 23

As summarized above, the claims of this group are directed to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal ion chelate resin including a second immobilized metal ion; and a

recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide.

In maintaining the rejection of the claims of this group, the Examiner asserts that it would have been obvious to one of skill in the relevant art to combine the expressed metal ion-binding tags of Tchaga et al. with the tandem columns of Porath et al.

With regard to establishing a *prima facie* case of obviousness, MPEP§2143 states:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Appellants respectfully submit that their is, in fact, no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references teachings in manner suggested by the Office.

Tchaga et al. teach adding an ion affinity peptide to the polypeptide of interest in order to efficiently complex metal ions, which increases specificity and adsorption affinity by preventing the participation of the native protein in adsorption. Specifically, Tchaga et al. is directed to the purification of a protein of interest using ion affinity tags, which constitute short polypeptide sequences that are designed to complex metal ions with much higher efficiency than the attached native polypeptide (please consult Tchaga et al., page 6, line 20 through page 7, line 4). The result is that the affinity of the fusion protein for the chromatographic column is mediated entirely by the metal ion binding capacity of the affinity tag itself, rendering the affinity for the column of the attached native polypeptide sequence irrelevant to the purification method, as taught by Tchaga et al., which states:

"There are numerous advantages of using a high affinity fusion protein. For example, the use of an affinity peptide ensures that no part of the native

protein of interest is involved in adsorption – the binding between the fusion protein and the ligand. At the same time, extremely high selectivity in the adsorption process is achieved." (Tchaga et al., page 2, lines 15-20)

In contrast, Porath et al. is directed to the purification of polypeptides to which no ion affinity tag has been fused, i.e. native, untagged proteins. Therefore, the purification process taught by Porath et al. depends entirely upon the affinity of various features of the native polypeptide sequence itself for the ion-loaded column (please consult Porath et al., page 1628, paragraph 8, *"Some Notes on the Adsorption Mechanism"*).

Accordingly, whereas in the method taught by Tchaga et al. purification must distinguish between tagged and untagged proteins, the tandem chromatography taught by Porath et al. must distinguish among native proteins, many of which may share comparable affinities for chelated metal ions.

Therefore, the methods of Tchaga and Porath address two distinct problems: Tchaga et al. that of using and maximizing the ion affinity of a polypeptide sequence specifically designed to bind metal ions (Tchaga et al., page 2, lines 15-20), and Porath et al. that of optimizing column conditions to isolate proteins whose metal-binding determinants are variable or unknown (Porath et al., page 1628, paragraph 8; page 1629, left column).

As such, the ordinarily skilled artisan would find no reason to combine the teachings of Tchaga et al. with those of Porath et al., since there is no reason to expect that a method directed to the purification of untagged proteins would provide an improvement in the purification of ion binding peptide-tagged proteins. The only document of record which teaches the success of such an approach is the instant Application.

In response to arguments made by the Appellants in the communication of February 28, 2006, and reiterated herein, the Examiner asserted, without evidentiary support, that "purification of proteins usually occurs in the presence of different columns ... and the use of additional columns (in tandem, for example) or different ions in the protocol is dictated by the need to optimize the conditions for most

efficient and maximum recovery of the protein of interest" (Office Action of August 10, 2006, page 4).

In the Response of August 10, 2006, the Appellants submitted that this reasoning does not support a motivation to combine references which teach different types of protein purification, and requested that, as provided for in MPEP 2144.03, "Reliance on Common Knowledge in the Art or 'Well Known' Prior Art", the Examiner provide evidence or an affidavit of personal knowledge as to why the person of ordinary skill in the relevant art would conclude such.

In response to arguments made by the Appellants in the communication of February 28, 2006, and reiterated herein, the Examiner additionally asserted, without evidentiary support, that "maximizing specificity and high-efficiency recovery go hand in hand in protein purification since, maximum specificity can cause high-efficiency of recovery, as it is desired when using any purification kit" (Office Action of August 10, 2006, page 5).

In the Response of August 10, 2006, the Appellants submitted that it is unclear why a relationship between specificity and high-efficiency recovery should be assumed to be identical for the tagged and untagged proteins as taught in the cited references, since specificity in the case of the tagged protein is overwhelmingly governed by the tag, as taught by Tchaga et al. Again as provided for in the rules, the Examiner was requested to provide evidence or an affidavit of personal knowledge as to why the person of ordinary skill in the relevant art would conclude such.

In responding to the Appellants' prior argument that there is no motivation to combine the cited references to be found in the references themselves, the Examiner merely reiterated what each reference teaches without showing where any motivation to combine is taught in those references or elsewhere (Office Action of August 10, 2006, pages 5-6). The Appellants submitted that the cited references are directed to two different strategies of protein purification, which were not combined in any document of record from the period of 1983 to 1998 for the reason that one of skill in the art had no reason to expect success in applying a strategy for purifying untagged proteins to a method teaching the use and optimization of ion-binding tags.

In the Advisory Action of November 27, 2006, the Examiner responds to the above arguments by asserting that the prior art is applicable for all the arguments mentioned in the Final office action, and that it is known in the prior art that affinity chromatography that utilizes metal binding incorporates a common technique (i.e., such as that described in Tchaga et al.: tagging with a designed ion affinity sequence, using a column packed with an ion to which the sequence binds). The Examiner further asserts that while this procedure which, as taught, uses a single column, is generally used for the purification of recombinant proteins with an engineered affinity tag, it can also be used for natural proteins with an inherent affinity for divalent cations.

The Appellants reply that the Examiner's response is not apposite to the issue at hand, which is why one of skill would apply a two-column method taught for use with native proteins to an ion-binding tagged protein taught as purified with a single column. The Examiner fails to address the argument that the point of including a designed ion-binding tag sequence is precisely to be rid of the effects of "inherent affinity," as plainly stated by Tchaga et al. (please consult Tchaga et al., page 2, lines 15-20).

Therefore, the ordinarily skilled artisan finds no motivation to combine the references, as discussed. If the motivation is not present in the references, then Examiner must provide extrinsic evidence that such motivation is found in knowledge generally available in the art or based upon established scientific principles. No such evidence is provided in the Advisory Action, nor in any Office communication of record.

The Advisory Action further states that protein purification utilizes different columns and different buffers in order to purify a protein of interest, and that in the purification process, a choice of a column or a buffer depends on the protein's size, physico-chemical property and binding affinity. Moreover, the Examiner indicates agreement with the Appellants that "the tagged status of the protein is relevant because it will dictate a proper choice of a column and a buffer (i.e. for tagged proteins a column with immobilized nickel ions in a resin is most appropriate, for example)."

Yet, in the subsequent paragraph, the Examiner responds to the Appellants' arguments that motivation to combine is absent, explicitly and implicitly, from the references by stating that MPEP 2144 allows that a rationale may be impliedly contained in the art or reasoned from knowledge generally available to one of ordinary skill or from established scientific principles.

Appellants have, in each communication, advanced arguments from the references which are consistent with general knowledge in the art and with established scientific principles. The references cited teach two strategies for protein purification, one of which relies upon intrinsic affinity of holoproteins for divalent cations and one of which relies overwhelmingly upon the affinity of a designed tag sequence which dominates the interaction of a protein with divalent cations. One of skill therefore would envision no reason to apply the method of the first to the proteins of the second.

The Examiner has provided no reasoning consistent with established scientific principles which would provide any motivation or suggestion to combine the teachings of the references, nor references in support thereof, but merely asserts without evidentiary support that the invention is obvious over "knowledge" common to the art.

As such, there is no motivation to combine the references in the manner suggested by the Examiner since the references are directed to the purification of different types of proteins and their is no evidence that applying Porath's method to the purification of Tchaga's tagged proteins would provide any benefit such that one would be motivated to make the Examiner suggested combination of teachings.

Accordingly, for at least these reasons Claims 11, 16 and 23 are patentable under 35 U.S.C. § 103(a) over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630). Reversal of the rejection is respectfully requested.

Group II: Claim 12

As noted above, the claims of this group are directed to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized metal ion; a second composition including a second metal

ion chelate resin including a second immobilized metal ion; in which the first metal ion is a hard metal ion, and the second metal ion is an intermediate metal ion; and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide.

The Examiner asserts that it would have been obvious to one of skill in the relevant art to combine the expressed ion-binding tags of Tchaga et al. with the tandem columns of Porath et al.

As discussed in detail above, Tchaga et al. teach adding an ion affinity peptide to the polypeptide of interest in order to efficiently complex metal ions, which increases specificity and adsorption affinity by preventing the participation of the native protein in adsorption. In contrast, Porath et al. describe the use of columns packed with chelator gels loaded with different metal ions in tandem in order to separate untagged serum proteins whose adsorption is mediated entirely by the native, i.e. untagged, protein.

Accordingly, as in the arguments for Group I above, the Appellants submit that neither the knowledge generally available to one of skill in the art nor the teachings of the cited references provide a basis to expect success in combining the teachings as suggested by the Examiner.

With regard to Claim 12, Tchaga et al. teach the purification of an ion-tagged affinity protein with a single column. Tchaga et al. are silent with regard to the use of more than one column, and therefore are silent with regard to the biophysical characteristics or identity of any particular pair of metal ions to be used a system of tandem columns.

The references fail to teach or suggest the use of a tandem pair of columns with specific characteristics of Claim 12 for the purpose of purifying an ion-binding tagged protein. Since Claim 12 is directed to a kit for purifying an ion-affinity tagged protein which includes metal ion chelate resins in which the first metal ion is a hard metal ion and the second metal ion is an intermediate metal ion, the reference fail to teach or suggest all of the elements of this claim and therefore Claim 12. Therefore, the rejection of Claim 12 may be withdrawn.

Group III: Claim 13

Claim 13 further specifies that the first metal ion is a hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}, and the second metal ion is an intermediate metal ion chosen from Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}.

The Examiner asserts that it would have been obvious to one of skill in the relevant art to combine the expressed ion-binding tags of Tchaga et al. with the tandem columns of Porath et al to arrive at the claimed invention.

In addition to the arguments provided above, with regard to Claim 13, Tchaga et al. teach the purification of an ion-tagged affinity protein with a single column. Tchaga et al. are silent with regard to the use of more than one column, and therefore are silent with regard to the biophysical characteristics or identity of any particular pair of metal ions to be used in tandem columns for the purification of a tagged protein.

Accordingly, since the instant claim is directed to a kit for purifying an ion-affinity tagged protein which includes metal ion chelate resins in which the first metal ion is a hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}, and the second metal ion is an intermediate metal ion chosen from Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}, the combined references fail to teach or suggest each and every element of Claim 13. Therefore, Claim 13 is not obvious over the cited combination of references and the rejection of Claim 13 may be withdrawn.

Group IV: Claims 18, 21 and 24

As noted above, the claims of this group are directed to a kit for purifying a protein, the kit including a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion, a second composition including a second metal ion chelate resin including a second immobilized metal ion, and a recombinant vector including a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for the metal ion affinity peptide.

The Examiner asserts that it would have been obvious to one of skill in the relevant art to combine the expressed ion-binding tags of Tchaga et al. with the tandem columns of Porath et al.

As discussed in detail above, Tchaga et al. teach adding an ion-affinity peptide to the polypeptide of interest in order to efficiently complex metal ions, which increases specificity and adsorption affinity by preventing the participation of the native protein in adsorption. In contrast, Porath et al. describe the use of columns packed with chelator gels loaded with different metal ions in tandem in order to separate untagged serum proteins whose adsorption is mediated entirely by the native, i.e. untagged, protein.

Accordingly, as in the arguments for Group I above, the Appellants submit that neither the knowledge generally available to one of skill in the art nor the teachings of the cited references provide a basis to expect success in combining the teachings as suggested by the Examiner.

With regard to Claims 18, 21 and 24, as discussed in detail in the arguments for Group I above, Tchaga et al. teach the purification of an ion-tagged affinity protein with a single column. Tchaga et al. are silent with regard to the use of more than one column, and therefore are silent with regard to the biophysical characteristics or identity of any particular pair of metal ions to be used in tandem columns for the purification of a tagged protein. Moreover, Porath et al. are silent with regard to a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion.

As such, as reviewed above with respect to the claims of Group I, there is no motivation to make the combination of teachings as asserted by the Examiner. Furthermore, even if the references are combined, all of the elements of the claims of this Group IV are not taught or suggested.

As such, the rejection of Claims 18, 21 and 24 may be withdrawn.

Group V: Claim 19

Claim 19 specifies the presence of a first composition including a first metal ion chelate resin including a first immobilized Co^{2+} metal ion and a second composition including a second metal ion chelate resin including a second immobilized hard metal ion.

Tchaga et al. are silent not only with regard to a second column, but also with regard to the biophysical characteristics or identity of any second metal ion to be used in a second, tandem column. Since Porath et al. teach neither the use of Co^{2+} in an affinity column nor the use of such a column in conjunction with a second column

including an immobilized hard metal ion, this silence by Tchaga et al. is not remedied by Porath et al.

As such, the combined references fail to teach or suggest each and every element of the instant Claim 19. Accordingly, the rejection of Claim 19 may be withdrawn.

Group VI: Claim 20

Claim 20 specifies the presence of a first metal ion chelate resin including a first immobilized Co^{2+} metal ion and a second immobilized hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}.

Tchaga et al. are silent not only with regard to a second column, but also with regard to the biophysical characteristics or identity of any second metal ion to be used in a second, tandem column. Since Porath et al. teach neither the use of Co^{2+} in an affinity column nor the use of such a column in conjunction with a second column including a second metal ion chelate resin including a second immobilized hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}, this silence by Tchaga et al. is not remedied by Porath et al.

Moreover, both Tchaga et al. and Porath et al. are silent with regard to a first composition including a first metal ion chelate resin in which the first metal ion is Co^{2+} and a second composition including a second metal ion chelate resin including a second immobilized hard metal ion chosen from Fe^{3+}, Ca^{2+} and Al^{3+}. As such, the combined references fail to teach or suggest every element of the claims and a *prima facie* case of obviousness is not made.

Accordingly, since the combined references fail to teach or suggest each and every element of the instant claim, Appellants submit that Claim 20 is patentable over the cited art.

In view of the arguments above, the Appellants submit that the combined teachings of Tchaga et al. and Porath et al. fail to make obvious the claims of Groups I-VI and respectfully request reversal of the rejection.

SUMMARY

I. Claims 11-13,16, 18-21 and 23-24 are not obvious under 35 U.S.C. § 103(a) over Tchaga et al. (WO 99/57992) in view of Porath et al. (Biochemistry, 1983: 22; p.1621-1630) because:

1) there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings in the manner suggested by the Office; and

2) the combined teaching of the references fails to teach or suggest all of the elements of claims.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 11-13, 16, 18-21 and 23-24 under 35 U.S.C. § 103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: February 6, 2007

By: _____
Bret Field
Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Ave., Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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CLAIMS APPENDIX

11. A kit for purifying a protein, said kit comprising:

a first composition comprising a first metal ion chelate resin comprising a first immobilized metal ion;

a second composition comprising a second metal ion chelate resin comprising a second immobilized metal ion; and

a recombinant vector comprising a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for inserting a heterologous nucleic acid molecule encoding a fusion partner protein for said metal ion affinity peptide.

12. The kit according to Claim 11, wherein the first metal ion is a hard metal ion, and the second metal ion is an intermediate metal ion.

13. The kit according to Claim 12, wherein the hard metal ion is chosen from Fe^{3+}, Ca^{2+} and Al^{3+}; and the intermediate metal ion is chosen from Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}.

16. The kit according to Claim 11, further comprising:

an extraction buffer;

a wash buffer; and

an elution buffer.

18. A kit for purifying a protein, said kit comprising:

a first composition comprising a first metal ion chelate resin comprising a first immobilized Co^{2+} metal ion;

a second composition comprising a second metal ion chelate resin comprising a second immobilized metal ion; and

a recombinant vector comprising a nucleotide sequence encoding a metal ion affinity peptide and at least one restriction endonuclease recognition sequence for

inserting a heterologous nucleic acid molecule encoding a fusion partner protein for said metal ion affinity peptide.

19. The kit according to Claim 18, wherein the second metal ion is a hard metal ion.

20. The kit according to Claim 19, wherein the hard metal ion is chosen from Fe^{3+}, Ca^{2+} and Al^{3+}.

21. The kit according to Claim 18, further comprising:
an extraction buffer;
a wash buffer; and
an elution buffer.

23. The kit according to Claim 11, wherein said metal ion affinity peptide comprises SEQ ID NO:1.

24. The kit according to Claim 18, wherein said metal ion affinity peptide comprises SEQ ID NO:1.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.